UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/677,653	10/03/2000	Peter Daniel Christian	A-58631-4/RFT/DJM	7496

7590 04/23/2003

Flehr Hohbach Test Albritton & Herbert
Four Embarcadero Center
Suite 3400
San Francisco, CA 94111

EXAMINER	
LUCAS, ZACHARIAH	
ART UNIT	PAPER NUMBER
1648	13

DATE MAILED: 04/23/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/677,653	CHRISTIAN ET AL.	
	Examiner	Art Unit	
	Zachariah Lucas	1648	

-- Th MAILING DATE of this communication app ars on the cover sheet with th correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-24* is/are pending in the application.

4a) Of the above claim(s) *24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Status of the Claims

1. Currently, claims 15-24 are pending in the present application. Claims 15-24 are under consideration, and were rejected in the prior action (mailed on June 6, 2002). Claim 24 has been withdrawn from consideration as to a non-elected invention.

2. Claims 17, 18, 21, and 22 were amended in the Response, received by the Office on December 11, 2002. It is noted that although claims 17, 21, and 22 were not marked as amended in the clean copy of the claims in the Response, they were so marked in the marked-up copy, and the clean copy of all the pending claims. The Amendments to all of these claims have therefore been entered, although the clean copy of the claims does not indicate that claims 17, 21, and 22 were amended.

3. The Art Unit location of your application, and the examiner to whom the case has been docketed in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Examiner Zachariah Lucas in Art Unit 1648.

4. This action is being made Non-Final because it raises new grounds of rejection not made in the prior action, and not necessitated by amendment.

Specification

5. **(Prior Objection- Withdrawn)** The application was objected to in the prior application for non-compliance with the rules regarding applications comprising amino acid or nucleic acid sequence disclosures. In view of the Sequence submissions filed with the Response, the objection is withdrawn.

6. **(Prior Objection- Maintained)** The specification was objected to in the prior Office action for not citing all of the parent application to which priority was claimed in the first paragraph of the application. This objection is maintained because, although the applicant has amended the first paragraph to name each of these parent applications, application 08/485,355 has been improperly identified as a continuation in part, rather than as a continuation, of application 08/440,522.

7. **(New Objection)** The disclosure is objected to because of the following informalities: it appears that the word "later" on line 17 of page 11 should be --larger--.

Appropriate correction is required.

Claim Objections

8. **(Prior Objection-Withdrawn)** The claims of the application were objected to because of the following informalities: they were not preceded by an introductory statement such as "what is claimed is," "we claim," or "that which is claimed is." This objection is withdrawn in view of the amendments made in the Response.

9. **(Prior Objection-Withdrawn)** Claim 18 was objected to in the prior action because of the following informalities: the format of the reference to SEQ ID NO: 50 was improper. The objection is withdrawn in view of the amendments made in the Response.

Claim Rejections - 35 USC § 112

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. **(Prior Rejection- Withdrawn)** Claims 15-23 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The applicant's arguments were persuasive.

12. **(Prior Rejection-Withdrawn)** Claim 17 was rejected in the prior action under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim was rejected for not providing the full name of the Helicovera armigera stunt virus prior to referring to it by the abbreviation HaSV. In view of the amendment to the claim in the Response, the rejection is withdrawn.

13. **(Prior Rejection-Withdrawn)** Claim 18 was rejected in the prior action under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim was

rejected for not identifying the source of the P71 protein in the claim. The applicant has amended the claim to further identify the protein by its source. Therefore, the rejection is withdrawn.

14. **(Prior Rejection- Withdrawn)** Claim 21 was rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim was rejection for indefiniteness regarding the terms "antisense sequence" and "mimicking structure." In view of the amendment to delete the phrase "mimicking structure" from the claim, and the arguments regarding the phrase "antisense sequence," the rejection is withdrawn.

15. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

16. **(Prior Rejection- Restated and Maintained)** Claims 15, 21, and 22 were rejected in the prior action under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. These claims read on nucleic acids comprising a first sequence encoding an insect RNA virus capsid protein, and a second sequence that either is, or encodes a protein that is, insecticidal. Among the insecticidal sequences claimed by the applicant are antisense sequences

and ribozymes. The claim was rejected because the applicant has provided no written description support for such ribozymes or antisense sequences. It is noted that claims 16-19 were inadvertently excluded from the rejection. The rejection is hereby restated the as a rejection against claims 15-19, 21, and 22.

The applicant has traversed this rejection on the grounds that "the invention may be practiced to deliver essentially any nucleic acid" and that "[s]ince a specific utility of the invention is the control of insect populations, however, the claims recite sequences which are either insecticidal or which encode toxins which are insecticidal." This traversal is not found persuasive. Rather, the very fact the applicant is arguing is the basis of the present rejection.

As was indicated in the prior action, the claims are drawn to genus of nucleic acids. As was also indicated in the prior action, in order to satisfy the 112 ¶1 written description requirement for a genus of DNA molecules, the applicant must provide more than a statement of the biological function of the DNA. See e.g. Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 U.S.P.Q.2d 1016, 1027 (CAFC 1991); and Fiers v. Revel, 25 U.S.P.Q.2d 1601, 1604-05 (CAFC 1993). In Amgen v. Chugai, the Court of Appeals for the Federal Circuit stated that "[i]t is not sufficient to define [a DNA] solely by its principal biological property, e.g. encoding of human erythropoietin." Id., at 1021. Rather, "what is necessary is that [the applicant] provide a disclosure sufficient to enable one skilled in the art to carry out the invention commensurate with the scope of his claims." Id., at 1027. In these statements, the court has expressly stated that a DNA molecule must be described by means of description other than by naming the encoded protein to satisfy the 112 ¶1 written description requirement.

In a later case, the court stated what forms of description the applicant could provide to provide their claims with written description support. See, Fiers v. Revel, 25 U.S.P.Q.2d at 1604-05. According to the CAFC, two methods of describing and claiming DNA are through the DNA's structural makeup (its sequence), or by a process of making it. Id. Finally, and more recently, the Federal Circuit again took this position. In the case University of California v. Eli Lilly and Co., 43 U.S.P.Q.2d 1398, at 1406 (1997), the court stated that defining a cDNA by its function "is only a definition of a useful result rather than a definition of what achieves that result." The court also stated that such a description "does not define any structural features commonly possessed by members of the genus [of claimed cDNAs] that distinguish them from others." Id. Thus, in order to support claims of the present application, the applicant must identify some structural characteristic or characteristics of the claimed nucleic acids.

However, the applicant has not done so. The applicant has identified a few representative sequences of the claimed nucleic acids, but has not identified any structure (or structures) that defines the claimed insecticidal nucleic acids sequences (or insecticidal proteins encoded by the sequences). Instead, exactly as the cases cited above have indicated may not be done, the applicant has identified the claimed nucleic acids solely on the basis of the functions of the nucleic acids- (i.e. they are or encode insecticidal molecules). In view of this, the applicant has not provided such a description of the claimed invention that one skilled in the art would have accepted that the applicant was in possession of the full scope of the claimed invention.

17. **(Prior Rejection- Reformed and Maintained)** Claims15-23 were rejected in the prior action under 35 U.S.C. 112, first paragraph, because the specification. While being enabling for

isolated nucleic acids comprising the a first sequence encoding an insect RNA virus capsid protein and a second sequence that encodes an insecticidal protein, or is itself an insecticidal molecule selected from the sequences disclosed as such on pages 14-15 in the specification, does not reasonably provide enablement for the claimed nucleic acids where the second sequence is any ribozyme, antisense, or other insecticidal nucleic acid. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. The claims have been described above. As claim 20 refers to a specific, and known insecticidal toxin, the rejection is withdrawn as to this claim. Therefore, the rejection is restated as applying against claims 15-19, and 21-23.

The Applicant's traversal of the rejection was on the basis that the applicant has enabled the administration of any nucleic acid into an insect. However, while the applicant may be enabled for nucleic acids generally, the applicant is claiming a specific subset of such nucleic acids. These nucleic acids are disclosed, and claimed, as comprising ribozymes and antisense molecules, and other insecticidal nucleic acids. As indicated above, the applicant has provided only a few examples of ribozymes, and has not otherwise provided any guidance that would lead one of ordinary skill in the art to any other such insecticidal nucleic acids. Because the applicant has not disclosed, or provided any guidance to, such other nucleic acids, the applicant is not enabled for claims to any insecticidal nucleic acid, but is limited to the specific embodiments disclosed in the application.

Further, while the applicant is generally not enabled for insecticidal nucleic acids, the applicant is also more particularly not enabled for any ribozymes or antisense sequences, other than the ribozymes disclosed in the application. With regards to the use of antisense molecules, a

recent (2002) article by Braasch et al. emphasizes that major obstacles persist in the art. See, Braasch et al., Biochemistry, 41(14): 4503-4510, at 4503, paragraphs 1 and 2 (stating, "gene inhibition by antisense oligomers has not proven to be a robust or generally reliable technology. Many researchers are skeptical about the approach, and it has been suggested that many published studies are at least partially unreliable"). Braasch goes on to identify factors that contribute to the unpredictable efficacy of antisense compounds *in vivo*: poor antisense oligonucleotide access to sites within the mRNA to be targeted, difficulties with delivery to and uptake by cells of the antisense oligos, toxicity and immunological problems caused by antisense oligos, and artifacts created by unpredictable binding of antisense compounds to systemic and cellular proteins.

Regarding the difficulties of predicting whether antisense oligonucleotides can access sites within their target mRNA, Braasch explains, "it has been difficult to identify oligonucleotides that act as potent inhibitors of gene expression, primarily due to difficulties in predicting the secondary structures of RNA. Id. A later article, by Branch et al. (TIBS, 23:45-50), adds that "internal structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules." Page 45, third column. Additionally, in a review of the potential use of antisense oligos as therapeutic agents (Gewirtz et al., PNAS 93: 3161-3163) teaches, on page 3161 (columns 2 and 3), that the inhibitory activity of an oligo depends unpredictably on the sequence and structure of the nucleic acid target site and the ability of the oligo to reach its target.

The uptake of oligonucleotides by cells has been addressed by Agrawal (TIBTECH 14:376-387), who states, "[o]ligonucleotides must be taken up by cells in order to be

effective....several reports have shown that efficient uptake of oligonucleotides occurs in a variety of cell lines, including primary cells whereas other reports indicate negligible cellular uptake of oligonucleotides. Cellular uptake of oligonucleotides is complex process; it depends on many factors, including the cell type, the stage of the cell cycle, the concentration of serum. It is therefore, difficult to generalize that all oligonucleotides are taken up in all cells with the same efficiency." Agrawal, at 378. On page 379 of the article, Agrawal further states that "microinjection or using lipid carriers to supply an oligonucleotide in cell culture increases the potency of the oligonucleotide in cell culture, but it is not clear how relevant this approach is for *in vivo* situations."

Braasch also discussed the non-specific toxicity effects of *in vivo* antisense administration, stating "even when active oligomers are discovered, the difference in oligonucleotide dose required to inhibit expression is often not much different than doses that lead to nonselective toxicity and cell death...oligonucleotides can bind to proteins and produce artifactual phenotypes that obscure effects due to the intended antisense mechanism" Page. 4503, paragraphs 1 and 2. Branch affirms that "non-antisense effects are not currently predictable, rules for rational design cannot be applied to the production of non-antisense drugs, These effects must be explored on a case by case basis" (Page 50), while a more recent article, by Tamm et al. (The Lancet 358: 489-497), states, on page 493, that "[i]mmune stimulation is widely recognized as an undesirable side-effect...the immunostimulatory activity of a phosphorothioate-modified oligonucleotide is largely unpredictable and has to be ascertained experimentally."

Further, Branch reasons that "the value of a potential antisense drug can only be judged after its intended clinical use is known, and quantitative information about its dose-response

curves and therapeutic index is available" (Page 46, second column). Tamm et al. concludes by stating that until "the therapeutic activity of an antisense oligonucleotide is defined by the antisense sequence, and thus is to some extent predictable...antisense will not be better than other drug development strategies, most of which depend on an empirical approach."

The specification of the instant application fails to provide adequate guidance for one of skill in the art to overcome the unpredictability and challenges of applying results from *in vitro* experiments to the *in vivo* treatment of disease, or *in vivo* methods of inhibition, as exemplified in the references above. The applicant has in fact, not provided any guidance to those in the art that would lead them to operable antisense oligonucleotides with insecticidal effects. Further, as ribozymes, being also oligonucleotides, have the same general mechanism as antisense molecules, only with the additional enzymatic activity, the above teachings apply equally for these nucleotide sequences. While the applicant has identified a few specific ribozymes, the applicant has not provided any guidance that would lead those wishing to practice the claimed invention to any further such sequences. Thus, the applicant is not enabled for insecticidal nucleic acids generally, and is specifically not enabled for any antisense sequences, or any ribozymes other than those disclosed.

For these reasons, and for the reasons of record, the rejection of claims 15-19, and 21-23 for exceeding the scope of enablement is maintained.

Claim Rejections - 35 USC § 102

18. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

19. **(Prior Rejection-Withdrawn)** Claims 15-23 were rejected in the prior action under 35 U.S.C. 102(b) as being anticipated by Christian et al., WO 94/04660. The claims describe isolated nucleic acids comprising a first sequence encoding at least one insect RNA virus capsid proteins, and a second sequence which is, or encodes a protein that is, insecticidal. The disclosed capsid protein is the P71 protein, SEQ ID NO: 50, of HaSV. Christian et al teaches such a nucleic acid. The Applicant traverses this rejection on the grounds that the applicant has priority to application 08/089,372, which predates the Christian reference. The traversal, and the argument regarding priority presented on page 7 of the Response, is found persuasive. The rejection is therefore withdrawn.

Claim Rejections - 35 USC § 103

20. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

21. **(Prior Rejections-Withdrawn)** Claims 15-23, and claim 18 were rejected in the prior action under 35 U.S.C. 103(a) as being unpatentable over, respectively, Wilcox et al. (U.S. Patent 6,051,556) in view of Hanzlik et al. (J. Gen. Virol. 74:1805-1810- hereinafter Hanzlik);

Wilcox in view of Hanzlik, and further in view of Hanzlik et al. (J. Gen. Virol. 74(4): 799-811- hereinafter Hanzlik 1995. The Applicant traversed each of these rejections for the same reasons as argued with respect to the Christian reference above (i.e. the priority claim to application 08/089,372). The traversal is found persuasive in that the applicant has demonstrated that the applicant predates the teachings by the Hanzlik references. As the applicant predates these references, and as Wilcox alone cannot support the rejections, the rejections are withdrawn.

22. **(Prior Rejection-Maintained)** Claims 15, 16, and 19-23 were rejected in the prior action under 35 U.S.C. 103(a) as being unpatentable over Wilcox in view of Harley et al. (Virology 69:323-326). The Applicant traversed this rejections for the same reasons as argued with respect to the Christian reference above (i.e. the priority claim to application 08/089,372). However, the traversal is not found persuasive in this instance.

The applicant has argued that Wilcox in view of Harley cannot be applied against the present application because Wilcox, with a filing date of May 10, 1995, cannot be used as prior art against the present claims, which claim priority to prior U.S. application 08/089,372, filed on July 8, 1993. This argument is not found persuasive because Wilcox qualifies as art under 35 U.S.C. 102(e). This means that this reference is considered as prior art as of its earliest priority date. See MPEP § 706.02. Because the Wilcox patent claims priority back, as a continuation, to a prior application (07/983,344 filed on November 30, 1992), the Wilcox patent has priority back to at least the year 1992. As the Applicant points out, the present application has priority extending back to July 8, 1993. It is further noted that Wilcox claims priority as a CIP to patent 5,290,914, with a filing date of April 28, 1988. The teachings relied on in the present rejection

are also taught in this patent. See, abstract; column 1, lines 10-15, and 40-45; and column 3, lines 8-16. Thus, the applicant's assertion that the Wilcox reference is not available as prior art against the present application is without merit. The rejection is therefore maintained.

Conclusion

23. No claims allowed.

24. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachariah Lucas whose telephone number is 703-308-4240. The examiner can normally be reached on Monday-Friday, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 703-308-4027. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Z. Lucas
Patent Examiner
April 14, 2003

JAMES HOUSEL 4/21/03
SUPERVISORY PATENT EXAMIN
TECHNOLOGY CENTER 160(